Remarks/Arguments

The foregoing amendments include the cancellation of non-elected claims and Claim 42, and the amendment of claims 40 and 59. Support for the newly added phrase "non-oligomeric" is at least at page 2, line 2 of the specification. The term "covalent" is supported throughout the specification, such as, for example, at page 4, lines 15-20, and page 20, lines 15-19. The current amendments do not add new matter.

Priority Claims and New Matter Rejection

The claims under examination in this application before the present amendment (Claims 40-43 and 45-51) were accorded only the filing date of the present application (February 20, 2002). In addition, Claims 40-43 and 45-51 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application had possession of the claimed invention. In explaining this new matter rejection, the Examiner pointed out that applicants did not show where support for the new claims added in the Preliminary Amendment dated February 20, 2002 was found in the specification.

Applicants submit that all claims currently pending are fully supported by the specification as originally filed and are, therefore, entitled to the priority of June 26, 1998. For the Examiner's convenience, locations for supported are indicated in the table below.

Claim	Phrase	Support
40	non-oligomeric	at least at page 2, line 2
40	less than 2000 daltons in size	at least at page 16, line 26
40	-SH group, masked -SH group, or activated -SH group	at least at page 6, lines 10-21
40	covalent target protein-ligand conjugate	at least at page 4, lines 15-20; and page 20, lines 15-19
40	disulfide exchange conditions	at least at page 27, lines 17-26
41	less than 1500 daltons	at least at page 16, line 27
43	less than 750 daltons	at least at page 16, line 27
45 and 46	presence of reducing agent	at least at page 6, lines 10-21;

		page 20, lines 27-32; and page 27, lines 17-26
47	2-mercaptoethanol	at least at page 27, lines 23-24, and page 20, line 30
48	mass spectrometry	at least at page 21, lines 7-25

From the foregoing table it should be clear that all claims under examination are fully supported by the specification as originally filed, therefore, the present application should be accorded the priority of June 26, 1998, and the new matter rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

Status of the Claims and Restriction/Election of Species

Applicants note that the previous restriction requirement has been withdrawn, and the election of species requirement has been made final. It is believed that, upon entry of the present amendment, claims 59 and 60 will read on the elected species, therefore, their examination in the present application is respectfully requested.

In addition, Applicants submit that the prior art cited by the Examiner does not anticipate or render obvious the elected species, accordingly, it is anticipated that, under the provisions of MPEP § 803.02, the search will be extended to the non-elected species, and the genus claims will be allowed within the full scope of the claims currently pending.

Claim Rejections - 35 U.S.C. §102

Claims 40-43, and 45-51 were rejected under 35 U.S.C. § 102(b) "as being anticipated" by Erlanson *et al.*, PNAS **August 15, 2000**, 97(17), 9367-9372. Since all claims pending are fully entitled to the priority of **June 26, 1998** of parent application Serial No. 09/105,372 (now U.S. Patent No. 6,335,155), Erlanson *et al.* is not prior art, and the present rejection should be withdrawn.

Claim Rejections - 35 U.S.C. § 103

(1) Claims 40-43 and 45-47 were rejected under 35 U.S.C. § 103(a) "as being unpatentable" over Paalman *et al.*, Nucleic Acid Research 1997, 25(9), 1795-1801 and Liem *et al.*, J. Mol. Biol. 1993, 231, 950-959.

The rejection is respectfully traversed.

Paalman *et al.* reports the formation of a covalent complex between a methylguanine methyltransferase protein and an oligonucleotide by using a thiol-containing guanine analog linker that forms a cross-link between the oligonucleotide and the active site cysteine of the methylguanine methyltransferase. DNA, and in particular oligonucleotides, are oligomeric proteins. Accordingly, Paalman *et al.* does not teach a method for identifying a *non-oligomeric* ligand of a protein, as claimed in the present application. In addition, Paalman *et al.* does not teach a method that combines a target protein with a "ligand *candidate*," as recited in step b) of claim 40. Since methylguanine methyltransferase is a known DNA repair protein, and is known to bind DNA, DNA is not a ligand *candidate*, rather a known binding partner (substrate) of methylguanine methyltransferase. In other words, the method described by Paalman *et al.* does not *identify* ligands of the target protein by contacting the protein with one or more ligand candidates, rather reports the formation of a stabilized complex between a target protein and its *known substrate*, which can be used for biochemical studies, which would not be possible with the normal reactive complex formed in nature. In addition, Paalman *et al.* does not teach the use of mass spectrometry to detect the complex formed between methylguanine methyltransferase and its oligonucleotide substrate (claims 48-51, and claim 60).

Liem *et al.* does not cure the deficiencies of Paalman *et al.* Liem *et al.* describes experiments directed to the study of factors influencing the repair of the mutagenis lesion of O^6-methylguanine in DNA by methylguanine methyltransferase. Just as in Paalman *et al.*, the complexes formed are between a protein and a known oligomeric substrate of the protein. Although the DNA substrates studied by Liem *et al.* are shorter in size, this does not change the fact that they are oligomeric, unlike the ligand candidates and ligands of the present invention.

Liem *et al.* does not teach the use of mass spectrometry to detect the complex formed between methylguanine methyltransferase and its oligonucleotide substrates (claims 48-51, and claim 60).

Accordingly, the closest teaching of the combination of Paalman *et al.* and Liem *et al.* is that the DNA repair protein methylguanine methyltransferase is capable of forming stable complexes with shorter oligonucleotide substrates, which can then be used to study the mechanism and kinetics of DNA repair.

The cited combination contains no suggestion or hint whatsoever that would indicate that previously unidentified ligands of any protein can be identified by using a disulfide chemistry, and there is nothing in the cited combination of references that would suggest a method of identifying non-oligomeric small molecule ligands of any protein. Since the combination of Paalman *et al.* and Liem *et al.* does not make obvious the invention claimed in the present application, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 40-43 and 45-51 were rejected under 35 U.S.C. § 103(a) "as being unpatentable" over Paalman *et al.*, and Liem *et al.*, and Ganem *et al.*, J. Am. Chem. Soc. 1991, 113(16), 6294-6.

Paalman *et al.* and Liem *et al.* were applied as in the previous rejection. Ganem *et al.* was cited for its disclosure of mass spectroscopy for "identifying enzyme-substrate, receptor-ligand . . . complexes). According to the rejection, it would have been obvious to one skilled in the art at the time the invention was made to "identify" a "ligand" that binds to a "target protein" under reducing conditions, by mass spectroscopy. The Examiner asserts that one skilled in the art would have been motivated to use the mass spectrometers as taught by Ganem *et al.* with the ligand-receptors taught by the combined teachings of Paalman *et al.* and Liem *et al.* due to a statement cited from Ganem *et al.*, page 6294, second paragraph.

Applicants respectfully disagree.

The combination of Paalman *et al.* and Liem *et al.* has been discussed in response to the previous rejection. Ganem *et al.* teaches the use of mass spectrometry for detection of enzyme-substrate, receptor-ligand, and antibody-antigen complexes "whose weak *noncovalent* interactions constitute the essential basis of molecules recognition in the biological world." Indeed, the objective of the paper is to provide means for the detection of "*noncovalent* molecular association complexes . . . under conditions of real-time reaction monitoring." This is in contrast to the claims of the present application, which describe the detection of a *covalent* target protein-ligand conjugate, e.g. by mass spectrometry.

Paalman et al. and Liem et al. cannot be properly combined with Ganem et al.

Since both Paalman *et al.* and Liem *et al.* disclose covalent complexes, their combination with Ganem *et al.*, the teaching of which is specific to non-covalent complexes, is improper. One skilled in the art would not be motivated to combine the teaching of Ganem *et al.* specifically addressing issues associated with the detection of non-covalent molecular interaction complexes, with the teaching of Paalman *et al.* and/or Liem *et al.* where the described complexes are covalent, therefore, stability is not an issue. In addition, Paalman *et al.* and Liem *et al.* discuss protein-DNA complexes, while Ganem *et al.* is directed to protein small molecule interactions, which yield noncovalent protein-small molecule complexes. As protein-DNA complexes and protein-small molecule complexes pose different issues, this difference is another reason why the purported combination is improper.

Paalman et al. and Liem et al., and Ganem et al., even if their combination were proper, do not make obvious the claimed invention

As discussed above, Paalman *et al.* and Liem *et al.* fail to describe the *identification* of a ligand that forms a covalent disulfide bond with a target protein *by testing ligand candidates.* Since Ganem *et al.* has no disclosure for making or identifying *covalent* complexes between a target protein and a ligand, or the identification of new ligands from among ligand candidates, it does not make up for the deficiencies of the two primary references.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Double Patenting

Claims 40-43 and 45-47 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-12 of U.S. Patent No. 6,335,155 B1. The attached Terminal Disclaimer is believed to overcome this rejection.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should the Examiner find that there are any further issues outstanding, Applicants hereby request a personal interview. The Examiner is respectfully requested to contact the undersigned attorney to arrange the time fot eh interview.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0002DV1C2). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: April 18, 2003

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